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TITLE: New antiinflammatory pro-drugs - comprises anti-inflammatory agent bonded to polysaccharide

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BASIC-ABSTRACT:

Antiinflammatory prodrugs of formula PS-O-A-(CH2)n-B-D (I) and their salts are new: (where PS-OH = dextran, carboxymethyl dextran, diethylaminoethyl dextran, starch, hydroxyethyl starch, alginate, glycogen, pullulan, agarose, cellulose, chitosan, chitin or carrageenan, with a molecular wt. (Mw) of 40,000-5,000,000; A = CO or a direct bond; n = 0-14; B = O, CO, NR or a direct bond; R = H or lower alkyl; D = R1CO or R2O; R1COOH and R2OH = antiinflammatory agents; provided that R1COOH is not acetylsalicylic acid when PS-OH = dextran, A = a direct bond, n = = and B = a direct bond).

USE/ADVANTAGE - (I) are used for treating rheumatism, arthritis, gout, ulcerative colitis, etc. They give localised sustained release of DH on parenteral admin. and selective release of DH in the terminal ileum and colon on oral admin.

EQUIVALENT-ABSTRACTS:

Antiinflammatory prodrugs of formula PS-O-A-(CH2)n-B-D (I) and their salts are new: (where PS-OH = dextran, carboxymethyl dextran, diethylaminoethyl dextran, starch, hydroxyethyl starch, alginate, glycogen, pullulan, agarose, cellulose, chitosan, chitin or carrageenan, with a molecular wt. (Mw) of 40,000-5,000,000; A = CO or a direct bond; n = 0-14; B = O, CO, NR or a direct bond; R = H or lower alkyl; D = R1CO or R2O; R1COOH and R2OH = antiinflammatory agents; provided that R1COOH is not acetylsalicylic acid when PS-OH = dextran, A = a direct bond, n = = and B = a direct bond).

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DRAWING:

TITLE-TERMS: NEW ANTIINFLAMMATORY PRO DRUG COMPRISE ANTI INFLAMMATION AGENT BOND POLYSACCHARIDE

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(54) **High molecular weight prodrug derivatives antiinflammatory drugs.**

(57) Compounds of the formula 1

$PS-O-A-(CH_2)_n-B-D$ (1)

wherein PS-O represents an alkoxide residue of any of the free hydroxy groups of a polysaccharide (PS-OH) compound with molecular weight (M_w) of from 40,000 to 5,000,000 selected from dextran, carboxymethyl dextran, diethylaminoethyl dextran, starch, hydroxyethyl starch, alginates, glycogen, pullulan, agarose, cellulose, chitosan, chitin and carrageenan,
A is a carbonyl group or absent,
n is zero or a positive integer from 1 to 14,
B is oxygen, a carbonyl group, NR wherein R is hydrogen or lower alkyl, or B is absent, and
D is

(i) a group of the formula:

R_1-CO- (1_1)

wherein R_1-CO- represents the acyl residue of a carboxylic acid drug (R_1-COOH) used in the treatment of inflammatory disorders; or (ii) a group of the formula:

R_2-O- (1_2)

wherein R_2-O- refers to the C-21 alkoxide residue of a known antiinflammatory steroid (R_2-OH) or an alkoxide residue of any other drug or medicament containing a hydroxy functional group used in the treatment of inflammatory disorders; with the proviso that when A is absent, n is 0, and B is absent, then R_1-CO- is different from the acyl residue of acetylsalicylic acid;
and non-toxic pharmaceutically acceptable acid addition salts thereof;
and non-toxic pharmaceutically acceptable cation salts thereof.

Such compounds are biolabile prodrugs providing controlled release and prolonged duration of action of the parent active antiinflammatory agents locally at the administration site after intra-articular, intra-muscular, subcutaneous or extra-dural application while at the same time being highly stable in

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aqueous solution in the pH range 3-5. After oral administration of such prodrugs the parent drug is liberated selectively in the terminal ileum and the colon over an extended period of time.

Description

HIGH MOLECULAR WEIGHT PRODRUG DERIVATIVES OF ANTIINFLAMMATORY DRUGS

Background of the invention

Field of the invention

The present invention relates to novel high molecular weight prodrug forms of drugs useful in the treatment and the relief of pain of conditions characterized by inflammation, such as rheumatism, arthritis, gout and ulcerative colitis, to methods for preparing the prodrug forms, to pharmaceutical compositions containing such prodrug forms, and to methods for using the prodrug forms.

For purposes of this specification, the term "prodrug" denotes a derivative of a known and proven antiinflammatory agent (e.g. naproxen, ibuprofen, ketoprofen, hydrocortisone, 5-aminosalicylic acid, methylprednisolone etc.) which derivative, when administered to warm-blooded animals, including humans, is converted into the proven drug. The enzymatic and/or chemical hydrolytic cleavage of the compounds of the present invention occurs in such a manner that the proven drug form (parent drug compound) is released, and the moiety or the moieties split off remain nontoxic or are metabolized so that nontoxic metabolites are produced.

In these novel prodrug forms the antiinflammatory drug compounds have been linked covalently to certain biodegradable polysaccharide derivatives either directly through ester linkages or by intercalating between the drug and the polysaccharide carrier a suitable spacer arm. After parenteral administration these novel prodrug forms combine a prolonged duration of activity, by slowly releasing the active antiinflammatory drug at the site of administration, with a desirably high stability in aqueous solution in the pH range 3 - 5 in vitro. Due to the molecular size of the polysaccharide carrier molecule the new prodrug forms are further characterized by a restricted mobility in vivo, thus allowing the active drug compound to be regenerated in a localized manner at the administration site in the vicinity of the diseased tissue. After oral administration to warm-blooded animals of such prodrug conjugates prolonged and localized release of the parent active agent takes place in the terminal ileum and in the colon effected by glucosidases and hydrolases situated in that part of the GI-tract. Besides providing selective delivery to the terminal ileum and the colon after oral administration, the prodrug conjugates give rise to therapeutically effective and constant concentration of the released active drugs in the blood over an extended period of time. Furthermore the new prodrug forms are endowed with a desirably high water-solubility at pH 3-5 in comparison to the parent antiinflammatory drug compounds. It is still a further property of the prodrug derivatives that they exhibit a feasible tissue compatibility.

Description of the prior art

It is well known that a wide variety of drug compounds are used in the management of disorders characterized by inflammation. These drug compounds include non-steroidal antiinflammatory drugs (NSAIDs) which in this context are defined as derivatives of anthranilic acid, phenylalkanoic acids and indomethacin, such as naproxen, ketoprofen, ibuprofen, diclofenac and the like; corticosteroids such as hydrocortisone, prednisolone, methylprednisolone, triamcinolone and the like; antimalarials such as hydroxychloroquine and the like; immunosuppressives such as methotrexate, melphalan and the like; 5-aminosalicylic acid as well as other drug compounds having diverse biological properties and structures.

Disorders characterized by inflammation, which frequently are treated by the above mentioned drug compounds, include:

Synovitis

a. Adult and juvenile rheumatoid arthritis

b. Other collagen vascular disorders (e.g. systemic lupus erythematosus, mixed collective tissue disease syndrome)

c. Crystal-induced arthropaties (gout, pseudogout)

d. Seronegative spondyloarthropathies (peripheral joint involvement of ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome, inflammatory bowel disease)

e. Knee synovitis following hip arthroplasty

f. Acute trauma *Synovial cyst of Heberden's Nodes*

Adhesive capsulitis (frozen shoulder)

Shoulder-hand syndrome

Popliteal and antecubial cysts

Tendinitis

a. Supraspinatus, bicipital, wrist extensor, De Quervain's syndrome, flexor carpi radialis and ulnaris, digital flexor (trigger finger),

Achilles, semimembranosus *Bursitis*

a. Subacromial, coracoid, olecranon, trochanteric, anserine, prepatellar, infrapatellar, retiocalcaneal

Carpal,Guyon, and tarsual tunnel syndrome

Epicondylitis

Plantar fascitis

Temporomandibular joint syndromes
Osteoarthritis
a. Knee and inflammatory interphalangeal joint synovitis
b. First metacarpophalangeal, carpometacarpal, and metatarsophalangeal joints
c. Lumbar facet arthropathy *Ganglia*
Fibrositic trigger points
Low back syndrome
Tietze's syndrome
Costochondrosis
Xiphoiditis
Dupuytren's contracture
Rheumatoid nodules
Episacroiliac lipomate (Stockman's nodules)
Hand swelling of mixed connective tissue disease
Soft tissue flexion contractures (recent)
Sciatica
Acute lumbar disc prolapse
Ulcerative colitis
Crohn's disease

Other indications for the above mentioned antiinflammatory agents will be apparent for those skilled in the art.

In the management of inflammatory disorders, a medicinal need exists for new pharmaceutical parenteral formulations of antiinflammatory drugs, which after administration to warm-blooded animals locally in the vicinity of the inflamed tissue (for example intra-articular administration) provide liberation of the active inflammatory agent with a well-defined rate (*controlled release*) over an extended period of time (*prolonged duration of action*) at the site of administration (*localized drug action*). This need exists because conventional formulations of antiinflammatory drugs used hitherto in the treatment of inflammatory disorders suffer from several drawbacks. After oral administration of NSAIDs, only a small amount of the instilled dose gains access to the inflamed tissue (for example to inflamed joints) (Gallo et al. (1986); Mäkela et al. (1981)). Since the duration of activity of NSAIDs are limited, frequent administration of massive amounts of NSAIDs is therefore necessary in order to maintain therapeutically effective concentrations of NSAIDs locally at the diseased site. This administration pattern in turn results in undesirable side-effects such as microvascular blood loss from the GI tract and gastric ulcers (Baker and Rabinowitz (1986) and references cited therein).

Furthermore a low-level NSAID therapy, provided by localized and prolonged duration of action, is strongly needed since most side-effects associated with NSAID therapy are dose-related. This is the case for the above mentioned damage of the gastrointestinal mucosa, which in addition is systemic in nature (Baker and Rabinowitz (1986); Bjarnason et al. (1984)). Another serious dose-dependent side-effect is the significant mental status change of elderly while taking a variety of NSAIDs (Baker and Rabinowitz (1986) and references cited therein).

Microcrystalline aqueous suspensions of corticosteroids are available for intra-articular administration. The crystals are retained within the joint and dissolve slowly producing a sustained antiinflammatory effect. However, a significant amount of the instilled dose leaches to the systemic circulation in an uncontrolled manner producing serious side-effects such as suppression of endogenous cortisol production (Hunneyball (1986); Gray and Gottlieb (1983)). In addition the crystal preparation, per se, give rise to local flare reactions due to the physical nature of the drug formulation (Gray and Gottlieb (1983); Hunneyball (1986)).

Since antiinflammatory drug therapy is associated with several and severe side-effects, the development of drug formulations to achieve a localized, low-level, prolonged-effect therapy would represent a major advantage (Hunneyball (1986) and references cited therein). The need for drug formulations with these desirable attributes has been generally recognized (Ratcliffe et al. (1987)). Apart from the application of corticosteroid suspension, attempts to achieve local and prolonged duration of action after intra-articular injection include incorporation of antiinflammatory drugs in liposomes (Dingle et al. (1978)) and in microspheres (Ratcliffe et al. (1984); Ratcliffe et al. (1987)). These colloidal approaches suffer from several drawbacks and differ considerably from the approach and the compounds of the present invention.

Human inflammatory bowel diseases such as ulcerative colitis and Crohn's disease are currently treated by oral administration of prednisolone or sulfasalazine. The latter drug is assumed to be cleaved in the lower bowel by anaerobic bacteria to yield the therapeutically active 5-aminosalicylic acid. Oral therapy by using formulations of these drugs suffers from several drawbacks mainly due to the non-specific absorption of the drugs along the gastrointestinal tract (Thomas et al. (1985); Brown et al. (1983)). Consequently, in order to obtain effective concentrations of the drugs at the diseased site, high doses have to be given which in turn leads to severe local as well as systemic side effects. Thus, the limitations to the use of sulfasalazine are for example the development of adverse gastrointestinal, hematological, and generalized side effects, or more serious reactions, including agranulocytosis, toxic epidermal necrolysis, parestesia, hepatotoxicity, pancreatitis, pulmonary disease and male infertility (Brown et al. (1983)). High molecular weight prodrugs of 5-aminosalicylic acid by using synthetic macromolecular carriers have been synthesized with the aim to transport the active agent selectively to the colon (US patent 4,190,716, US patent 4,298,595). However,

regeneration of 5-aminosalicylic acid from the latter prodrugs in vivo was poor.

In view of the foregoing, it is quite obvious that a serious need exists for improved parenteral and oral formulations of antiinflammatory drugs which will overcome the aforementioned disadvantages. From the foregoing, it also appears that successful high molecular weight prodrug forms of antiinflammatory drugs should be retained at the site of administration or should deliver the parent drug selectively to the inflamed tissue (for example within a joint cavity), should be tissue compatible and finally should lead to a controlled release and prolonged duration of action of antiinflammatory drugs at the diseased site.

Summary of the invention

It is an object of the present invention to provide such derivatives of antiinflammatory drugs which are prodrugs designed to cleave in such a manner as to enable the original parent drug form to be released at its target site or sites of activity, while the remaining cleaved moiety is nontoxic and/or is metabolized in a nontoxic fashion.

It is another object of the present invention to provide novel high molecular weight prodrug types of antiinflammatory drugs characterized by possessing prolonged duration of activity by slowly and in a controlled and predictable manner releasing the active antiinflammatory drug in vivo. The prodrug forms are further characterized by exhibiting a desirably high stability in aqueous media in the pH range 3 - 5 in vitro.

It is a further object of the present invention to provide novel bioreversible derivatives for antiinflammatory drugs which derivatives, when administered intra-articularly to warm-blooded animals, remain in the joint cavity or by endocytosis are taken up by the inflammatory cells in the synovium, thus combining localized drug action with a sustained release of the active drug compound.

It is still another object of this invention to provide novel prodrug forms of antiinflammatory drugs which derivatives, when given to warm-blooded animals by local parenteral administration in the vicinity of other tissues characterized by inflammatory disorders, provide localized and prolonged drug action at the site of administration.

It is still another object of this invention to provide novel prodrug forms of antiinflammatory drugs which derivatives, when given orally to warm-blooded animals, regenerate the parent drug compound selectively in the terminal ileum and in the colon over an extended period of time (localized and sustained release formulations).

It is yet another object of this invention to provide novel prodrug forms of antiinflammatory drugs which derivatives, when given orally to warm-blooded animals, result in sufficiently high and constant concentration of the released active drug in the blood over an extended period of time (sustained release formulations).

It is yet another object of this invention to provide high molecular weight prodrug types of antiinflammatory drugs which derivatives, when administered to warm-blooded animals, elicit the bio-affecting/pharmacological response characteristic of the drugs from which they are derived, yet which are characterized in being less irritating to the tissues surrounding the administration site.

Other objects, features and advantages of the invention will be apparent to those skilled in the art.

The foregoing objects, features and advantages are provided by the novel compounds of formula 1

$$PS - O - A - (CH_2)_n - B - D \quad (1)$$

wherein PS - O represents an alkoxide residue of any of the free hydroxy groups of a polysaccharide derivative (PS - OH) as defined below,

A is a carbonyl group or absent,

n is zero or a positive integer from 1 to 14,

B is oxygen, a carbonyl group, NR wherein R is hydrogen or lower alkyl, or B is absent, and

D is

(i)

R_1-CO- (1_1)

wherein R_1 - CO - represents the acyl residue of a carboxylic acid drug or medicament (R_1 - COOH) used in the treatment of inflammatory disorders;

(ii)

R_2-O- (1_2)

wherein R_2-O- refers to the C-21 alkoxide residue of a known antiinflammatory sterold (R_2-OH) or an alkoxide residue of any other drug or medicament containing a hydroxy functional group used in the treatment of inflammatory disorders; and nontoxic pharmaceutically acceptable acid addition salts thereof;

and nontoxic pharmaceutically acceptable cation salts thereof.

In the present context the term "polysaccharide" applies to carbohydrate polymers that contain periodically repeating structures in which the dominant interunit linkage is of the O-glycosidic type. In the present invention the macromolecular carriers used for the antiinflammatory drugs are polysaccharides such as dextran, starch and the like; derivatives thereof such as carboxymethyl dextran, diethylaminoethyl dextran, hydroxyethyl starch and the like; alginates, glycogen, pullulan, agarose, cellulose, chitosan, chitin, carrageenan and the like. In the present application, PS-OH signifies any such polysaccharide carrier compound.

The polymer backbone of the polysaccharides and their derivatives described in this invention differ slightly in chemical structure. However, prodrug conjugates containing identical ligands but are derived from various

of the aforementioned polysaccharides behave similarly to the dextran conjugates of the antiinflammatory drugs defined in formula 1 as regards condition of synthesis, physico-chemcial properties and biological activity. Thus, this invention includes the use of dextran, starch, hydroxyethyl starch as well as the other aforementioned polysaccaride derivatives as feasible macromolecular carriers for antiinflammatory drugs.

The dextrans are high molecular weight polysaccharides made up of α-D-anhydroglucopyranosidic units and characterized in that the linkage between the monomeric units are of both α-1,6 and non-α-1,6 type, at least 50% of these linkages being of the α-1,6 type.

A striking feature of the dextrans is the wide variations they exhibit with respect to their physical and structural properties including molecular weight, molecular weight distribution, molecular structural repeating α-1,6 to non-α-1,6 linkages ratio, and the water sensitivity. As to the latter property, while the so-called "native dextrans", being hydroxylbearing substances, are hydrophilic, some of the dextrans are readily soluble in water whereas others are difficultly soluble in water, are initially swollen thereby and only ultimately, if at all, completely dissolved therein.

A wide variety of dextrans may be used in practicing this invention, which, as stated above, concerns the use of dextrans as carriers for antiinflammatory drugs. The dextran used may have a molecular weight of from 5,000 to 150 x 10^6 as determined by light scattering measurements, a molecular structural repeating α-1,6 to non-α-1,6 linkages ratio of from 1.9:1 to 30:1; a polydispersity of from 1.1 to 10 as defined as the ration M_w/M_n, where the M_w and M_n refer to the weight average molecular weight and the number average molecular weight, respectively; and be soluble or substantially insoluble in water depending on the use for which the specific drug carrier is intended.

The dextrans may be obtained by various methods. They may be synthesized from sucrose by enzyme action in the presence or substantially absence of bacteria. For example, an aqueous nutrient medium containing sucrose, particularly nitrogenous compounds and certain inorganic salts, may be inoculated with a culture of an appropriate microorganism such as those of the *Leuconostoc mesenteroides* and *L. dextranicum* types, and incubated at the temperature most favourable to the growth of the microorganism until maximum dextran production is attained. This is synthesis of the dextran from sucrose by the so-called "whole culture" method, i.e., the synthesis is effected by enzyme action in the presence of the bacteria and cellular debris. Or the culture obtained by cultivating the Leuconostoc bacterium may be filtered to isolate the enzyme (dextransucrase) which occurs in the filtrate. The filtrate, usually after dilution to predetermined enzyme potency, may be mixed with an aqueous sucrose solution, and the mixture may be allowed to stand under controlled conditions of pH and temperature until the dextran is synthesized. The enzyme may be separated from the filtrate and used in powdered condition or in the form of an aqueous solution, usually the latter. This is dextran synthesis by enzyme action in the substantial absense of bacteria and cellular debris.

The dextran obtained initially by these procedures is so-called "native" dextran which normally has a very high average molecular weight, calculated to be in the millions. It may be precipitated from the medium in which it is synthesized by the addition of an organic liquid which is a non-solvent for the dextran. The non-solvent, or precipitant, may be a water-miscible aliphatic alcohol, e.g. methanol, ethanol or isopropanol, or a ketone such as acetone, or dioxane. The precipitated dextran may be purified and dried to a substantially white mass which may be reduced to powdered condition for use in the synthesis.

Native or high molecular weight dextran may be hydrolyzed under acid or neutral conditions, or by enzyme action to a molecular weight lower than that of the native material. Thus "clinical" dextran has an average molecular weight of from 20,000 or 200,000. In "clinical" dextran production, when the desired molecular weight is obtained by hydrolysis or cleavage of the native material, it is usual to isolate the "clinical" product from the hydrolysate by fractional precipitation according to which, by successive addition of increasing amounts of water-miscible alcohol or ketone, the highest molecular weight fraction is first thrown down and separated, and the desired or intermediate molecular fraction is then precipitated and recovered. This procedure leaves a supernatant containing dextran the average molecular weight of which is below the "clinical" range, and the supernatant is usually discarded as waste. The different dextran fractions may also be isolated from the hydrolyzate by fractional solution methods involving the use of the precipitant in conjunction with a dextran solvent, usually water. It may be noted, here, that when the dextran synthesis is effected by the action of the enzyme on sucrose in the absence of bacteria, it is possible to carry out the synthesis under conditions such as to favor the production of dextran of relatively low molecular weight in at least preponderant proportion. It is possible, therefore, as is now known, to obtain relatively low average molecular weight dextran by direct enzymatic synthesis from sucrose. Furthermore, after repeated gelfiltration of the isolated dextran fractions, using for example the Sephadex® series, dextran products with a polydispersity as low as 1.1 may be obtained. When dextran is synthesized from sucrose by enzyme action, in the presence or substantial absence of bacteria and cellular debris, the water-sensitivity of the native dextran obtained is influenced by the microorganism cultivated to obtain the culture, or enzyme isolatable therefrom, introduced into the sucrose-bearing medium in which the dextran is to be synthesized. Thus, native dextrans synthesized by the use of the microorganisms bearing the following NRRL (Northern Regional Research Laboratories) classification, or their enzymes, are quite readily soluble in water: *Leuconostoc mesenteroides* B-512, B-1146, B-119, and B-1196. These dextrans are, usually, smooth, lustrous, elastic gums which are quite readily soluble in water to give clear or substantially clear solutions.

The native dextrans from the microorganisms (or their enzymes) (NRRL) *Leuconostoc mesenteroides* B-742, B-1191, B-1208, and B-1216, and from *Streptobacterium dextranicum* B-1254 are, generally speaking,

rather rough, dull, non-elastic gums which may be regarded as relatively insoluble in water but which are water-swellable and go into solution in water under heating and stirring to give viscous solutions that are somewhat turgid.

A third group of native dextrans is represented by and includes those obtained from microorganisms (or their enzymes) bearing the NRRL classifications: *Leuconostoc mesenteroides* B-1120, B-1144, B-523, and *Betabacterium vermiforme* B-1139. These dextrans are generally more or less flocculent gums, which are swellable by water but which are, for all practical purposes, substantially insoluble therein.

Polysaccharides including dextrans contain a huge number of hydroxy groups available for covalent attachment of organic substances, hereinafter called "ligands". In dextran predominantly the hydroxy groups of the monomeric α-D-glucose unit at the position C-2, C-3, C-4 are available for ligand fixation, but also the free hydroxy groups at the position C-6 of the terminal α-D-glucose units in the main chains as well as the side chains of dextran may be used for establishment of dextran-ligand bonds.

With regard to establishment of covalently linked ligands the polysaccharide hydroxy groups at the positions C-2, C-3, C-4 and C-6 differ only slightly in reactivity (de Belder and Norrman (1968); Larsen and Johansen (1985)). Furthermore in case of ligand attachment accomplished through polysaccharide ester formation the proportion in which ester bonds are formed at the C-2, C-3, C-4 and C-6 position is thermodymanically determined due to acyl migration (Casinovi et al. (1974)). Consequently no single hydroxy group of the monomeric carbohydrate unit is exclusively preferred for ligand fixation. Although the same ligand or different ligand types theoretically might occupy all the hydroxy groups of one single monomeric carbohydrate unit of the polysaccharide chain it is much more likely that independently of the synthesis conditions the covalently attached ligands will be distributed uniformly along the polysaccharide chains (Larsen and Johansen (1985)).

In the present context, the term "lower alkyl" designates C_{1-8} alkyl which may be straight or branched, such as methyl, ethyl, propyl, isopropyl, butyl, tert. butyl, pentyl, hexyl, heptyl, or octyl.

The term "nontoxic pharmaceutically acceptable acid addition salts" as used herein generally includes the nontoxic acid addition salts of compounds of formula 1, formed with nontoxic inorganic or organic acids. For example, the salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulphuric , sulphamic, nitric, phosphoric and the like; and salts with organic acids such as acetic, propionic, succinic, fumaric, maleic, tartaric, citric, glycolic, lactic, stearic, malic, pamoic, ascorbic, phenylacetic, benzoic, glutamic, salicylic, sulphuric, sulphanilic, and the like.

The term "nontoxic pharmaceutically acceptable cation salts" as used herein generally includes the nontoxic cation salts of compounds of formula 1, formed with nontoxic inorganic or organic bases. For example, the salts include those derived from cations such as potassium, sodium, calcium, magnesium, zink, chlorprocaine, diethanolamine, ethylendiamine, meglumine, procaine, diethylamine, piperazine, tromethamine, and the like.

As stated above, D in the formula 1 can represent the acyl residue R_1-CO- (in formula 1_1) of any drug, pharmaceutical or medicament (R_1-COOH), useful in the treatment of inflammatory disorders, having one or more carboxylic acid functions. Examples of drugs or pharmaceuticals from which the instant high molecular weight prodrugs are derived include but are not limited to:

a. Non-steroidal antiinflammatory agents like:

Sulindac: (z)-[5-fluoro-2-methyl-1-(4-methylsulphinylbenzylidene)inden-3-yl]acetic acid
Indometacin: 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid
Naproxen: (+)-2-(6-methoxy-2-napthyl)propionic acid
Fenoprofen calcium: calcium (±)-2-(3- phenoxyphenyl)propionate dihydrate
Ibuprofen: 2-(4-isobutylphenyl)propionic acid
Ketoprofen: 2-(3-benzoylphenyl)propionic acid
Indoprofen: 2-[4-(1-oxoisoindolin-2-yl)phenyl]propionic acid
Diflunisal: 5-(2,4-difluorophenyl)salicylic acid
Tolmetin sodium: sodium (1-methyl-5-p-toluoylpyrrol-2-yl)acetate dihydrate
Flurbiprofen: 2-(2-fluorobiphenyl-4-yl)propionic acid
Diclofenac sodium: sodium [2-(2,6-dichloroanilino)phenyl]acetate
Mefenamic acid: N-(2,3-xylyl)anthranilic acid
Flufenamic acid: N-(ααα-trifluoro-m-tolyl)anthranilic acid
Meclofenamic acid: N-(2,6-dichloro-m-tolyl)anthranilic acid
Fenclozic acid: 2-(4-chlorophenyl)-4-thiazoleacetic acid
Alclofenac: (4-allyloxy-3-chlorophenyl)acetic acid
Bucloxic acid: 3-(3-chloro-4-cyclohexylbenzoyl)propionic acid
Suprofen: α-methyl-4-(2-thienylcarbonyl)benzeneacetic acid
Fluprofen: 3'-fluoro-α-methyl-[1,1'-biphenyl]-4-acetic acid
Cinchophen: 2-phenylquinoline-4-carboxylic acid
Pirprofen: 2-[3-chloro-4-(3-pyrrolin-1-yl)phenyl]propionic acid
Cinmetacin" 5-methoxy-2-methyl-1-(1-oxo-3-phenyl-2-propenyl)-1H-indole-3-acetic acid
Acemetacin: 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid carboxymethyl ester
Ketorolac: (±)-5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid
Clometacin: [3-(4-chlorobenzoyl)6-methoxy-2-methyl-indol-1-yl]acetic acid
Ibufenac: 4-(2-methylpropyl)-benzeneacetic acid

Tolfenamic acid: N-(3-chloro-o-tolyl)anthranilic acid
Fenclofenac: [2-(2,4-dichlorophenoxy)phenyl]acetic acid
Prodolic acid: 1,3,4,9-tetrahydro-1-propyl-pyrano[3, 4-b]indole-1-acetic acid
Clonixin: 2-(3-chloro-o-toluidino)nicotinic acid
Flutiazin: 8-(trifluoromethyl)-10H-phenothiazine-1-carboxylic acid
Flufenisal: 4-(acetyloxy)-4′-fluoro-[1,1′-biphenyl]-3-carboxylic acid
O-(Carbamoylphenoxy)acetic acid
Zomepirac sodium: sodium [5-(4-chlorobenzoyl)-1,4-dimethylpyrrol-2-yl]acetate dihydrate
Niflumic acid: 2-(ααα-trifluoro-m-toluidino)nicotinic acid
Lonazolac: 3-(4-chlorophenyl)-1-phenyl-1H-pyrazole-4-acetic acid
Fenbufen: 4-(biphenyl-4-yl)-4-oxobutyric acid
Carprofen: (±)-6-chloro-α-methyl-9H-carbazole-2-acetic acid
Tiaprofenic acid: 2-(5-benzoyl-2-thienyl)propionic acid
Loxoprofen: α-methyl-4-[2-oxocyclopentyl)methyl]-benzeneacetic acid
Etodolac: 1,8-diethyl-1,3,4,9-tetrahydro-pyrano[3, 4-b]indole-1-acetic acid.
Alminoprofen: α-methyl-4[(2-methyl-2-propenyl)amino]-benzeneacetic acid
2-(8-Methyl-10,11-dihydro-11-oxodibenz[b,f]oxepin-2-yl) propionic acid
4-Biphenylacetic acid

b. 4-Quinolone antibiotics like:

Ciprofloxacin: 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid
Norfloxacin: 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid
Acrosoxacin: ethyl-1,4-dihydro-4-oxo-7-(4-pyridyl)quinoline-3-carboxylic acid
Pipemidic acid: 8-ethyl-5,8-dihydro-5-oxo-2-(pyrrolidin-1-yl)pyrido[2,3-d]pyrimidine-6-carboxylic acid
Nalidixic acid: 1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid
Enoxacin: 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-1,8-naphthyridine-3-carboxylic acid
Ofloxacin: (±)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid
Oxolinic acid: 5-ethyl-5,8-dihydro-8-oxo-1,3-dioxolo[4,5-g]quinoline-7-carboxylic acid
Flumequine: 9-fluoro-6,7-dihydro-5-methyl-1-oxo-1H, 5H-benzo[ij]quinolizine-2-carboxylic acid
Cinoxacin: 1-ethyl-1,4-dihydro-4-oxo-[1,3]dioxolo4, 5-g]cinnoline-3-carboxylic acid
Piromidic acid: 8-ethyl-5,8-dihydro-5-oxo-2-(pyrrolidin-1-yl)pyrido[2,3-d]pyrimidine-6-carboxylic acid
Pefloxacin: 1-ethyl-6-fluoro-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid

c. Various other bio-affecting carboxylic acid agents:

Penicillamine: (-)-β,β-dimethylcysteine
5-Aminosalicylic acid
6-Aminocaproic acid
Methotrexate: 4-amino-10-methylfolic acid
Sodium cromoglycate: disodium 4,4′-dioxo-5,5′-(2-hydroxytrimethylenedioxy)di(4H-chromene-2-carboxylate)
Chlorambucil: 4-[4-bis(2-chloroethyl)amino-phenyl]butyric acid
Melphalan: 4-bis(2-chloroethyl)amino-L-phenylalanine
All-trans-retinoic acid
13-cis-retinoic acid
Salazosulfapyridine: 4-hydroxy-4′-(2-pyridylsulphamoyl)azobenzene-3-carboxylic acid
Azodisal sodium: disodium 3,3′-azobis[6-hydroxy]-benzoic acid
Gold sodium thiomalate
Furosemide: 4-chloro-N-fufuryl-5-sulfamoylanthranilic acid

As stated above, D in the formula 1 can also represent a C-21 alkoxide residue R_2-O- (in formula 1_2) of a known antiinflammatory steroid (R_2-OH) or an alkoxide residue of any other drug or medicament containing a hydroxy functional group, which is used in the management of inflammatory disorders. Examples of drugs or pharmaceuticals from which the instant high molecular weight prodrugs are derived include but are not limited to:

d. Antiinflammatory steroids like:

Hydrocortisone: 11β,17α,21-trihydroxypregn-4-ene-3,20-dione
Betamethasone: 9α-fluoro-16β-methylprednisolone
Dexamethasone: 9α-fluoro-16α-methylprednisolone
Prednisolone: 11β,17α,21-trihydroxypregna-1,4-diene-3,20-dione
Triamcinolone: 9α-fluoro-16α-hydroxyprednisolone
Fluocortolone: 6α-fluoro-11β,21-dihydroxy-16α-methyl-pregna-1,4-diene-3,20-dione
Cortisone: 17α,21-dihydroxypregn-4-ene-3,11,20-trione
Fludrocortisone: 9α-fluorohydrocortisone
Chloroprednisone: 6α-6-chloro-17,21-dihydroxy-pregna-1,4-diene-3,11,20-trione
Flumethasone: 6α,9α-difluoro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione
Fluprednisolone: 6α-fluoroprednisolone
Meprednisone: 16β-methylprednisone

Methylprednisolone: 6α-methylprednisolone
Paramethasone: 6α-fluoro-16α-methylprednisolone
Prednisone: 1,2-dehydrocortisone
Amcinafide: [11β,16α(R)]-9-fluoro-11,21-dihydroxy-16,17-[(1-phenylethylidene)bis(oxy)]-pregna-1,4-diene-3,20-dione
Clocortolone: (6α,11β,16α)-9-chloro-6-fluoro-11,21- dihydroxy-16-methyl-pregna-1,4-diene-3,20-dione
Desonide: 16-hydroxyprednisolone 16,17-acetonide
Desoximetasone: 9α-fluoro-11β,21-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione
Flunisolide: (6α,11β,16α)-6-fluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]-pregna-1,4-diene-3,20-dione
Fluocinolone acetonide: 6α,9α-difluoro-16α-hydroxyprednisolone acetonide
Triamcinolone acetonide: 9α-fluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione
Betamethasone 17-benzoate
Betamethasone 17-valerate

e. Various other bio-affecting hydroxy group containing agents:
1-Aurothio-D-glucopyranose
Hydroxychloroquine: 2-[N-[4-(7-chloro-4-quinolinylamino)pentyl]-N-ethylamino] ethanol sulphate
Amodiaquin: 4-(7-chloro-4-quinolinylamino)-2-(diethylaminomethylphenol dihydrochloride dihydrate
Quinine: (8α,9R)-6′-methoxy-cinchonan-9-ol

All of the above compounds are known in the art in the acid or salt form.

While all of the compounds encompassed by the formula 1 essentially satisfy the objectives of the present investigation, preferred compounds include those derived from the following compounds:

Sulindac
Naproxen
Fenoprofen
Ibuprofen
Ketoprofen
Indoprofen
Flurbiprofen
Mefenamic acid
Flufenamic acid
Meclofenamic acid
Fluprofen
Fenclofenac
Lonazolac
Fenbufen
Carprofen
Loxoprofen
5-aminosalicylic acid
Salazosulfapyridine
Azodisal sodium
Penicillamin
Chlorambucil
Melphalan
Gold sodium thiomalate
Furosemide
Hydrocortisone
Betamethasone
Dexamethasone
Prednisolone
Triamcinolone
Methylprednisolone
Triamcinolone acetonide
Aurothioglucose
Hydroxychloroquine
Amodiaquin
Quinine

Particularly preferred compounds of this invention include those wherein the acyl residue R_1-CO- is derived from one of the preferred acids named above, n is zero and A and B are absent. Furthermore, particularly preferred compounds include those wherein the alkoxy residue R_2 - O is derived from one of the preferred bio-affecting alcoholic drug compounds named above, A and B are carbonyl groups, n is 2, 3, 4, and PS - O is defined in connection with the general formula 1.

The especially preferred compounds are those particularly preferred compounds in which the polysaccharide carrier (PS - OH) is dextran or hydroxyethyl-starch of molecular weight in the range 40,000

-5,000,000. The degree of substitution (DS) of the high molecular weight prodrugs are in the range 0.1 - 35%, where DS is defined as the percentage of mg ligand released per mg of the high molecular weight prodrug.

Due to the considerable range of variation in the molecular weight of the drug molecule that can be attached to the polymer, it is advantageous to express the degree of substitution as the percentage of fraction of the free hydroxy groups in the polymer that has been bound to the moiety -A-$(CH_2)_n$-B-D in formula I. Since it is desirable that the compounds of formula I are soluble in water, the maximum useful degree of substitution will to a certain extent depend on the hydrophilic/lipophilic properties of the drug-containing moiety attached to the hydroxy group. Thus, the degree of substitution may be up to 1 of every 5 hydroxy groups, such as up to 1 out of every 10, for example up to 1 out of every 20, e.g. up to 1 out of every 30, alternatively up to 1 out of every 40, in some cases up to 1 out of every 50 hydroxy groups.

Detailed description of the invention

Dosage forms and dose

The high molecular weight prodrug compounds of formula 1 of the present invention can be used in the treatment and the relief of pain of any condition characterized by inflammation.

The prodrug compounds of formula 1 are designed to be administered parenterally in dosage forms or formulations containing conventional, nontoxic pharmaceutically acceptable carriers and adjuvants including microspheres and liposomes. The formulation and preparation of any of this spectrum of formulations into which the subject prodrugs can be disposed is well-known to those skilled in the art of pharmaceutical formulation. Specific formulation can, however, be found in the text entitled "Remington's Pharmaceutical Sciences", Sixteenth Edition, Mack Publishing Company, 1980.

The pharmaceutical compositions containing the active ingredient are in the form of a sterile injection. To prepare the preferred compositions of this invention, the prodrugs are dissolved or suspended in a parenterally acceptable liquid vehicle. Among the acceptable vehicles and solvents that may be employed are water, water adjusted to pH of from 3.5 to 5.0 by addition of an appropriate amount of 0.1 N hydrochloric acid, 1,3-butanediol, Ringer's solution and isotonic sodium chloride solution. The aqueous formulation may also contain one or more preservatives, for example methyl, ethyl or n-propyl p-hydroxybenzoate. The preferred routes of administration are intra-articular, subcutaneous, intra-muscular and extra-dural.

The prodrug compounds of formula 1 are further designed to be administered orally in dosage forms or formulations such as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide a pharmaceutically elegant and palatable preparation.

Formulations for oral use include tablets which contain the active ingredients in admixture with non-toxic pharmaceutically acceptable excipients. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium chloride, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, potato starch, or alginic acid; binding agents, for example, starch, gelatin or acacia; and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions usually contain the active materials in admixture with appropriate excipients. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents which may be a naturally-occurring phosphatide, for example, lecithin; a condensation product of an alkylene oxide with a fatty acid, for example, polyoxyethylene stearate; a condensation product of ethylene oxide with a long chain aliphatic alcohol, for example, heptadecaethyleneoxycetanol; a condensation product of ethylene oxide with a partial ester derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate; or a condensation product of ethylene oxide with a partial ester derived from fatty acids and hexitol anhydrides, for example, polyoxyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example, methyl, ethyl or n-propyl p-hydroxybenzoate; and one or more colouring agents; one or more flavouring agents; and one or more sweetening agents such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example, arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example, beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.